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Interspecies Extrapolation Based on Mechanistic Determinants of Chemical Disposition

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ABSTRACT

Uncertainty factors are applied in methods developed by the Environmental Protection Agency (EPA) to derive dose-response estimates. The uncertainty factors are applied to account for uncertainties in defined extrapolations from the laboratory animal experimental data conditions to a dose-response estimate appropriate for the assumed human scenario. The conceptual difference between these uncertainty factors and safety factors is best illustrated by how uncertainty factors can be modified as scientific data inform our understanding of the key factors that influence chemical disposition and toxicity. Mechanistic data help describe the major factors influencing chemical disposition and toxicant-target tissue interactions, and should increase the accuracy of exposure-dose-response assessment. Mechanistic data on the determinants of inhaled chemical disposition were used to construct default dosimetry adjustments applied by the EPA in its inhalation Reference Concentration (RfC) methods. Because these adjustments account for interspecies dosimetric differences to some degree, the uncertainty factor for interspecies extrapolation was modified. A framework is presented that allows for incorporation of mechanistic data in order to ensure that required extrapolations are commensurate with the state-of-the-science. Future applications of mechanistic data to modify additional uncertainty factors are outlined.

Key Words: risk assessment, uncertainty, dosimetry, interspecies scaling

INTRODUCTION

Various regulatory agencies have historically developed health-based permissible levels of exposure, based on an evaluation of toxicity data and the application of

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Safety Factors (SFs). Lehman and Fitzhugh (1954) introduced the concept of an Acceptable Daily Intake (ADI) to develop maximum allowable tolerance estimates for food additives or contaminants. These authors suggested that a No-Observed-Adverse-Effect Level (NOAEL) from a laboratory animal toxicology study could be extrapolated to human beings by division with a 100-fold SF to account for uncertainty in that extrapolation. These authors reasoned that uncertainty due to intraspecies and interspecies variability could each be addressed by a 10-fold factor. Thus, from its initiation, concepts of safety and uncertainty in the accuracy of the attendant extrapolations have been confounded. As the practice of applied toxicology advanced, variations and expansions on this approach appeared; most to include revisions or extensions by other factors to address additional sources of uncertainty previously not specified (*e.g.*, extrapolation of less-than-lifetime studies). Support for the various factors was garnered from empiric analyses and was not based on mechanistic understanding of underlying processes.

In 1983, the National Academy of Sciences (NAS) published a report entitled "Risk Assessment in the Federal Government: Managing the Process" (National Research Council, 1983). The NAS had been charged with evaluating the process of risk assessment as performed at the federal level in order to determine the "mechanisms to ensure that government regulation rests on the best available scientific knowledge and to preserve the integrity of scientific data and judgements." The NAS recommended that the scientific aspects of risk assessment should be explicitly separated from the policy aspects of risk management. This report marks the onset of current emphasis on clarifying the differences between safety and uncertainty factors, *i.e.*, application of a safety factor as a risk management or policy approach versus a factor for uncertainty due to limitations in the scientific database.

Based on the NAS report, methods developed subsequently by the U.S. Environmental Protection Agency (USEPA) to derive oral Reference Doses (RfDs) or inhalation Reference Concentrations (RfCs) incorporated an important conceptual departure from methods utilizing SFs (Barnes and Dourson, 1988; USEPA, 1994a). These EPA methods employ uncertainty factors (UFs) that are applied to account for uncertainties in defined extrapolations from the laboratory animal experimental data conditions to a dose-response estimate appropriate for the assumed human scenario. Although the application of uncertainty factors that are generally the same magnitude as those factors employed in safety factor approaches may appear to be semantic, the conceptual departure has two important aspects that result in quantitative differences.

The first aspect is that the intended use of an estimate for either dose-response characterization or for risk management influences its derivation (Jarabek and Segal, 1994). Often dose-response estimates are compared inappropriately with risk management or regulatory values that are intended to address different exposure scenarios and target populations or that are derived using additional considerations such as available control technology or economic impact (cost-benefit). An RfD or RfC is a dose-response estimate according to the NAS paradigm. The UFs are applied for extrapolations required for dose-response analysis only.

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The second aspect is that it is difficult to construct a strategy for changing the magnitude of a given SF because SFs are not applied with a consistent rationale. A 100-fold SF may be applied for various reasons from chemical to chemical, and the rationale is often not documented adequately. In contrast, the UFs employed in the RfD and RfC approaches readily allow for mechanistic data to improve the accuracy of a required extrapolation, and an opportunity for reduction of the specific factor because the UFs are applied for defined extrapolations. The UFs can be modified as scientific data inform our understanding about the factors influencing the disposition and toxicity of a chemical while SFs, if applied strictly as a matter of science policy, may not benefit from an improved knowledge base as readily. Emphasis on the need for flexibility in assigning the magnitude of UFs has been echoed by other authors (Lewis, Lynch, and Nikiforov, 1990; Renwick, 1993).

This presentation will focus on the methods used to derive RfC estimates for inhalation exposures. It outlines how data on the mechanistic determinants of inhaled chemical disposition have been utilized to construct dosimetry adjustments that account for interspecies differences in inhaled chemical disposition. A framework is presented to incorporate mechanistic data in an iterative fashion in order to ensure that the process is commensurate with available data. This framework is also used to illustrate the rationale for the resultant reduction in the magnitude of the UF applied for interspecies extrapolation. Analogous potential future applications of mechanistic data to address other UFs are outlined. Although this presentation is limited to discussion of inhalation assessments, the principles are applicable to additional exposure routes (oral or dermal) and all toxicity (noncancer and cancer).

GENERAL UF-BASED APPROACH

By definition, a database for derivation of a dose-response estimate for noncancer toxicity should ensure that both appropriate and adequate numbers of end points have been evaluated. Table 1 shows that the minimum requirement for derivation of an RfC with low confidence is a well-conducted subchronic inhalation bioassay that evaluates a comprehensive array of end points, including an adequate evaluation of respiratory tract effects, and establishes an unequivocal NOAEL and Lowest-Observed-Adverse-Effect Level (LOAEL) (USEPA, 1994a). Chronic inhalation bioassay data in two different mammalian species, developmental studies in two different mammalian species, and a two-generation reproductive study may be required to establish a high confidence RfC. The rationale supporting these database requirements is that all potential end points at various critical life stages must be evaluated, since the objective of the RfC is to serve as a lifetime estimate. Well-defined and conducted subchronic toxicity studies are considered to be reliable predictors of many forms of chronic toxicity, with the notable exceptions of carcinogenic, developmental, and reproductive effects. The specific requirement for adequate respiratory tract evaluation arises from the increased potential for the portal-of-entry tissue to interact intimately with chemicals. Dosimetry data that indicate distribution to extrarespiratory tract sites is insignificant (e.g., a highly reactive and irritant gas which causes respiratory tract damage) may obviate the requirement for reproductive and developmental data. This consideration of

Table 1. Minimum animal bioassay database for various levels of confidence in the inhalation Reference Concentration (RfC).

Mammalian Database[a]	Confidence	Comments
1. A. Two inhalation bioassays[b] in different species	High	Minimum data base for high confidence
B. One two-generation reproductive study		
C. Two developmental toxicity studies in different species		
2. 1A and 1B, as above	Medium to high	
3. Two of three studies, as above in 1A and 1B; one or two developmental toxicity studies	Medium to high	
4. Two of three studies, as above in 1A and 1B	Medium	
5. One of three studies, as above in 1A and 1B; one or two developmental toxicity studies	Medium to low	
6. One inhalation bioassay[c]	Low	Minimum data base for estimation of an RfC

[a] Composed of studies published in refereed journals, final quality assured/quality checked and approved contract laboratory studies, or core minimum Office of Pesticide Programs-rated studies. It is understood that adequate toxicity data in humans can form the basis of an RfC and yield high confidence in the RfC without this database. Pharmacokinetic data that indicate insignificant distribution occurs remote to the respiratory tract may obviate requirements for reproductive and developmental data.
[b] Chronic data.
[c] Chronic data preferred but subchronic acceptable.

mechanistic aspects of dosimetry is an example of how mechanistic data can aid in interpretation of data and influence the magnitude of a UF applied. If these minimum database requirements are not met, an RfC is not derived (USEPA, 1994a).

The basic equations used in derivation of an RfC from laboratory animal data are as follows. First, because many inhalation toxicity studies using laboratory animals are intermittent exposure regimens, a concentration (C) times time (t) product (C x t) prorate adjustment is used to normalize these exposures to a continuous exposure as:

$$\text{NOAEL}^*_{[ADJ]} \ (mg/m^3) = E \ (mg/m^3) \ D \ (h/day/24 \ h) \ W \ (days/7 \ days) \quad (1)$$

where the NOAEL$^{\bullet}_{[ADJ]}$ is the NOAEL or analogous effect level obtained with an alternate approach such as the benchmark dose (BMD) approach,[1] adjusted for duration of experimental regimen; E is the experimental exposure level; D is the number of (hours exposed/day)/24 h; and W is the number of (days of exposure/week)/7 days. The above duration adjustment is also applied to LOAELs. The rationale for this duration adjustment is that the resultant continuous human exposure concentration should be the (C x t) equivalent of the laboratory animal exposure level. Consideration of the basis of this adjustment is beyond the scope of this presentation and has been reviewed elsewhere (Jarabek, 1995a). An advantage of Physiologically Based Pharmacokinetic (PBPK) models is that the use of this duration adjustment is obviated because they incorporate and integrate various physicochemical and physiological determinants of chemical disposition, and thus dynamically simulate intermittent or continuous exposures.

The RfC methods then calculate the Human Equivalent Concentration (HEC) by applying a Dosimetric Adjustment Factor (DAF$_r$) to the laboratory animal exposure effect level in order to account for species differences in dosimetry as:

$$NOAEL^{\bullet}_{[HEC]} \ (mg/m^3) = NOAEL^{\bullet}_{[ADJ]} \ (mg/m^3) \ DAF_r \qquad (2)$$

where NOAEL$^{\bullet}_{[HEC]}$ is the NOAEL or analogous effect level obtained with an alternate approach such as the BMD, dosimetrically adjusted to an HEC; NOAEL$^{\bullet}_{[ADJ]}$ is defined in Equation 1; and DAF$_r$ is a dosimetric adjustment factor for either an effect in a specific respiratory tract region, r (ET, extrathoracic; TB, tracheobronchial; PU, pulmonary; TH, thoracic; or TOTAL, the entire tract) or a remote effect. The DAF$_r$ is either the Regional Deposited Dose Ratio (RDDR$_r$) for particles or the Regional Gas Dose Ratio (RGDR$_r$) for given gas category and type of effect (USEPA, 1994a).

The DAF$_r$ is a multiplicative factor that represents the laboratory animal to human ratio of a particular inhaled dose. The HEC is expected to be associated with the same delivered dose to the observed target tissue as in the laboratory species. The DAF$_r$ calculated depends on (1) the physicochemical characteristics of the inhaled toxicant (particle or one of three gas categories), (2) the location of the observed toxicity (i.e., either one of three respiratory tract regions or at remote sites), and (3) the type of dosimetry model (default or optimal) available for a particular chemical (Jarabek, 1995b). The DAF$_r$ is constructed using default normalizing factors for the physiological parameters of interest. For example, because insoluble particles deposit and clear along the surface of the respiratory tract, the deposited dose in a specific region (e.g., TB) is commonly normalized to the surface area of that region. Extrarespiratory or remote effects are often normalized to body weight.

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[1] Applied dose- or concentration-response modeling, known as the "benchmark dose" approach, was proposed as an improvement on the NOAEL/LOAEL approach by Crump (1984). In general terms, it is the use of a specific mathematical model (e.g., Weibull, logistic, polynomial) to determine a concentration associated with a predefined outcome (e.g., 10% response of a dichotomous outcome). Guidance on the application of this approach to derivation of RfD and RfC estimates is presented elsewhere (Barnes et al., 1995; USEPA, 1995). The use of the BMD approach does not obviate the requirement for UFs, with the exception of the UF for LOAEL to NOAEL extrapolation.

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Once the HEC is calculated, the UF shown in Table 2 are applied (as required) to calculate the RfC as:

$$RfC = NOAEL^{\cdot}_{[HEC]} / (UF\ MF) \qquad (3)$$

The UFs are generally an order of magnitude, although as discussed, incorporation of dosimetry adjustments or other mechanistic data has routinely resulted in the use of reduced UFs for RfCs. The composite UF applied to an RfC will vary in magnitude, depending on the number of extrapolations required. An RfC will not be derived when use of the available data involves more than four areas of extrapolation. The composite UF, when four factors are used, is reduced from 10,000 to 3,000 in recognition of the lack of independence of these factors. The lack of independence is evident in Table 2, which shows the various pharmacokinetic and pharmacodynamic processes typically believed to be encompassed by each UF. The coalescing of the composite UF is also based on the knowledge that each individual factor is generally conservative from the standpoint of the behavior of the average chemical, and that the multiplication of four or five values of 10 is likely to yield unrealistically conservative RfCs (USEPA, 1994a). An additional Modifying Factor (MF) may also be applied when scientific uncertainties in the principal study for derivation are not explicitly addressed by the standard UFs. For example, an MF might be applied to account for poor exposure characterization.

At this time, the basis for the magnitude of the majority of UFs is empirical and has been derived from oral data. Empiric support for the intraspecies UF is based on analyses of the distribution of effect levels from single-dose oral data (Weil, 1972; Dourson and Stara, 1983) and on an analysis of human variability for key pharmacokinetic parameters (Hattis, Erdreich, and Ballew, 1987). Calabrese (1985) found that the 10-fold factor for intraspecies or intrahuman variability (10H) appeared to provide protection for up to about 80-95% of the population. Dourson and Stara (1983) supported a 10-fold factor for interspecies extrapolation based on differences in milligrams per kilogram body weight doses due to different body-surface areas between experimental animals and humans. Dourson and Stara (1983) invoked studies by Evans, Harris, and Bunker (1944) and Hayes (1967) as empiric support for this interspecies extrapolation UF, although these analyses were not necessarily able to separate interspecies variability from intraspecies variability. Support for the 10-fold factor for subchronic to chronic extrapolation is based on analyses of the ratios of effect levels; *i.e.*, the distribution of ratios of NOAELs from 90-day studies compared to NOAELs from chronic studies was constructed and evaluated (Dourson and Stara, 1983; Weil and McCollister, 1963; Weil *et al.*, 1969). McNamara (1976) also demonstrated that a 10-fold factor accounted for 95% of the range of subchronic to chronic NOAEL ratios for the orally-administered compounds he evaluated. However, recent analyses of both oral and inhalation data by Nessel *et al.* (1995) support the use of less than a 10-fold factor for subchronic to chronic data extrapolation for either route. The LOAEL/NOAEL ratio for oral toxicity data after either subchronic or chronic exposures supports a 10-fold factor for this extrapolation (Weil and McCollister, 1963; Dourson and Stara, 1983). Dourson, Knauf, and Swartout (1992) performed similar analyses to support the 10-

Table 2. Guidelines for the use of Uncertainty Factors in Deriving Inhalation Reference Concentration (RfC)

Standards Uncertainty Factors (UFs)	Processes Considered in UF Purview
H = Human to sensitive human Use ≤ 10-fold factor when extrapolating from valid experimental results from studies using prolonged exposure to average healthy humans. This factor is intended to account for the variation in sensitivity among the members of the human population	Pharmacokinetics/pharmacodynamics Sensitivity Differences in mass Activity pattern Does not account for idiosyncracies
A = Laboratory animal to human Use ≤ 3-fold factor when extrapolating from valid results of long-term studies on laboratory animals when results of studies of human exposure are not available or are inadequate. This factor is intended to account for the uncertainty in extrapolating animal data to the case of average healthy humans. Use of a factor of "3" is recommended with default dosimetric adjustments. More rigorous adjustments may allow additional reduction. Conversely, judgment that the default may not be appropriate could result in an application of a 10-fold factor.	Pharmacokinetics/pharmacodynamics Relevance of laboratory animal model Species sensitivity
S = Subchronic to chronic Use ≤ 10-fold factor when extrapolating from less than chronic results on experimental animals or humans when there are no useful long-term human data. This factor is intended to account for the uncertainty in extrapolating from less than chronic NOAELs to chronic NOAELs.	Accumulation of chemical or damage Pharmacokinetics/pharmacodynamics Severity of effect Recovery Duration of Study Dependence of effect on duration
L = LOAEL$_{(HEC)}$ to NOAEL$_{(HEC)}$ Use ≤ 10-fold factor when deriving an RfC from a LOAEL$_{(HEC)}$, instead of a NOAEL$_{(HEC)}$. This factor is intended to account for the uncertainty in extrapolating from LOAEL$_{(HEC)}$ to NOAEL$_{(HEC)}$s.	Severity Pharmacokinetics/pharmacodynamics Slope of dose response curve Relationship of endpoints Functional vs. histopathological evidence (Sensitivity of Assay)
D = incomplete to complete database Use ≤ 10-fold factor when extrapolating from valid results in laboratory animals when the data are "incomplete". This factor is to account for the inability of any single animal study to adequately address all possible adverse outcomes in humans.	Lack of second species Data gaps (Lack of potential endpoints) Comprehensiveness of critical and supporting studies

Modifying Factor (MF)

Use professional judgement to determine whether another uncertainty factor (MF) that is ≤ 10 is needed. The magnitude of the MF depends upon the professional assessment of scientific uncertainty of the study and data base not explicitly treated above (e.g. the number of animals tested or quality of exposure characterization). The default value for the MF is 1.

Note: Assuming the range of the UF is distributed lognormally, reduction of a standard 10-fold UF by half (i.e., 10$^{.5}$) results in a UF is 3. Composite UF for derivation involving four area of uncertainty is 3,000 in recognition of the lack of independence of these factors and the inherent conservatism of multiplying multiplying several 10-fold factors together. Inhalation reference concentrations are not derived if all five areas of uncertainty are invoked.

fold UF applied to account for data gaps; specifically, reproductive and developmental toxicity studies and additional toxicity data in a second species. The requirement for data in a second species is also supported by analyses that have shown the common lack of concordance for target tissues across species (Appelman and Feron, 1986; Heywood, 1981; 1983).

Because of differences in dosimetry between the oral and inhalation routes, empiric support for the UFs applied in the RfC methods should utilize inhalation data only, and such analyses are underway. Further, because the different types of toxicity (portal-of-entry in the respiratory tract versus remote sites) may have different mechanistic determinants, the appropriate magnitude for these two types of toxicity of inhalation exposures should be determined separately. In addition, analyses should be performed using estimates derived with procedures that can account for the influence of sample size and spacing of exposure levels (*e.g.*, use of BMD estimates rather than NOAELs).

This presentation will now discuss the basis of the dosimetry adjustments used for interspecies extrapolation, and the rationale for the reduction of the UF applied for interspecies as applied in the RfC methods.

MECHANISTIC DETERMINANTS OF COMPARATIVE INHALED DOSE

This section provides a brief overview of the major mechanistic factors that control the inhaled dose of a given chemical. Extensive discussion of these factors is beyond the scope of this paper, but the overview is intended to impart an appreciation of the types of factors required in model structures aimed at characterizing inhaled dose. Differences in dosimetry are viewed as part of the rationale for the application of the UF for interspecies extrapolation.

The various species used in inhalation toxicology studies that serve as the basis for dose-response assessment do not receive identical doses in a comparable respiratory tract region, r (ET, TB, PU, TH, or the entire tract) when exposed to the same aerosol or gas (Brain and Mensah, 1983). Such interspecies differences are important because the adverse toxic effect is likely to be related more to the quantitative pattern of deposition within the respiratory tract than to the exposure concentration. This pattern determines not only the initial respiratory tract tissue dose, but also the specific pathways by which the inhaled material is cleared and redistributed (Schlesinger, 1985).

Disposition encompasses the processes of deposition, absorption, distribution, metabolism, and elimination. Differences in ventilation rates, and in the upper respiratory tract (URT) structure, and in size and branching pattern of the lower respiratory tract between species result in significantly different patterns of particle deposition and gas transport due to the effect of these geometric variations on air flow patterns. Disposition varies across species and with the respiratory tract region. For example, interspecies variations in cell morphology, numbers, types, distributions, and functional capabilities contribute to variations in clearance of initially deposited doses. Physicochemical characteristics of the inhaled particle or gas also influence the disposition and interact with the anatomic and physiologic parameters such as

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ventilation rate, cardiac output (perfusion), metabolic pathways, tissue volumes, and excretion pathways. The relative contributions of these processes with the physicochemical characteristics are affected by the exposure concentration and duration.

Initial deposition occurs for gases as well as particles because contact with the respiratory tract surface precedes absorption. The major processes affecting gas transport involve convection, diffusion, absorption, dissolution, and chemical reactions. The bulk movement of an inhaled gas in the respiratory tract is induced by a pressure gradient, and is termed convection. Convection can be broken down into components of advection (horizontal movement of a mass of air relative to the airway wall) and eddy dispersion (air mixing by turbulence so that individual fluid elements transport the gas and generate flux). Molecular diffusion is superimposed at all times on convection due to local concentration gradients. Absorption removes gases from the lumen and affects concentration gradients. Chemical reactions in the respiratory tract can increase absorption by acting as a sink to drive the concentration gradient. Systemic metabolism can also drive the concentration gradient for insoluble gases that are removed from the respiratory tract tissue by perfusion. Thus, the disposition of inhaled gases is influenced by the rate of transfer from the environment to the tissue, the capacity of the body to retain the material, and elimination of the parent and metabolites by chemical reaction, metabolism, exhalation, as well as excretion.

The physicochemical characteristics of the inhaled particles or gases also interact with these anatomical and physiological factors. For particle exposures, mass mean aerodynamic diameter (MMAD) and the distribution of the particle diameters about that mean are major determinants of deposition. Properties such as hygroscopicity and solubility influence deposition and clearance, respectively. Highly water-soluble and reactive gases are likely to react with tissues in the respiratory tract, whereas disposition of insoluble gases are more influenced by systemic factors such as perfusion and metabolism.

FRAMEWORK FOR INTERSPECIES DOSIMETRY ADJUSTMENTS

As discussed above, the interspecies extrapolation UF has historically been based on analyses of ratios of observed effect levels among species, as well as a theoretical basis on body-surface area scaling. The brief discussion on comparative inhalation dosimetry, however, should impart an appreciation that integration of the various physicochemical characteristics of inhaled agents (*i.e.*, at a minimum, particle versus gas) with the species-specific anatomic and physiologic parameters is necessary for estimating the respiratory tract surface deposition and absorbed dose in order to assess respiratory and extrarespiratory toxicity, respectively (Jarabek *et al.*, 1990). Adjustments for differences in delivered dose must be made before data array analysis of dose-response estimates, particularly across species, is performed. That is, NOAEL(HEC) estimates must be calculated first and then compared among species in order to determine the critical effect.

The term "exposure-dose-response" has been recommended to replace "dose-response" in order to be more accurate and comprehensive (Andersen *et al.*, 1992). Because the tissue dose of the putative toxic moiety is not always proportional to the

applied dose of a compound, emphasis has been placed on the need to distinguish clearly between exposure concentration and dose to critical target tissues. "Exposure-dose-response" assessment refers not only to the determination of the quantitative relationship between exposure concentrations and target tissue dose, but also to the relationship between tissue dose and the observed or expected responses in laboratory animals and humans. The process of characterizing the exposure-dose-response continuum is achieved by linking the mechanisms of critical biological factors that regulate the occurrence of a particular process and the nature of the interrelationships among these factors.

As illustrated in Figure 1, it is ultimately desirable to have a comprehensive biologically based dose-response model that incorporates the mechanistic determinants of chemical disposition, toxicant-target interactions, and tissue responses integrated into an overall model of pathogenesis. Unfortunately, the data to construct such comprehensive model structures do not exist for the majority of chemicals. Without dosimetry, default methods for dose-response estimation are limited to the rudimentary ("black-box") level and necessarily incorporate large uncertainty factors to ensure that the estimates are protective in the presence of substantial data gaps. This framework provides for the iterative incorporation of mechanistic data to characterize components along the exposure-dose-response continuum. For example, data on determinants of uptake and chemical disposition can inform our understanding of relevant tissue dose. With each progressive level, incorporation and integration of mechanistic determinants allow elucidation of the exposure-dose-response continuum and, depending on the knowledge of model
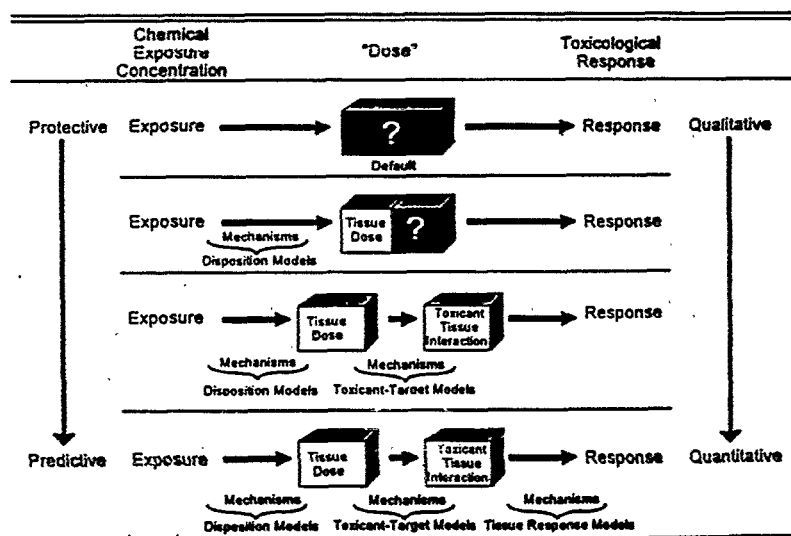

Figure 1. Schematic characterization of comprehensive exposure-dose-response continuum and the evolution of protective to predictive dose-response estimates.

parameters and fidelity to the biological system, a more accurate characterization of the pathogenesis. Due to the increase accuracy of the characterization with each progressive level, dose-response estimates also progress from more conservative (protective) to more factually-based (predictive) (Jarabek, 1995b).

Mathematical dosimetry models[2] that incorporate mechanistic determinants of disposition of chemicals have been useful in describing relationships between exposure concentration and target tissue dose, particularly as applied to describing these relationships for the dose-response component of risk assessment (Andersen et al., 1987). The default dosimetric adjustments used in the RfC methods were based on detailed dosimetry model structures which were reduced to forms requiring a minimal number of parameters by describing the dominant determinants of disposition for various categories of compounds and the use of simplifying assumptions (Jarabek, 1995b; USEPA, 1994a).

For example, because a theoretical model of particle deposition requires detailed information on all of the influential parameters (e.g., respiratory rates, exact airflow patterns, and complete measurement of the branching pattern of the respiratory tract) across the various species used in risk assessment, an empirical model (i.e., a system of equations fit to experimental data) was developed as the default model (USEPA, 1994a). The deposition data of Raabe et al. (1988) were used because the same nose-only exposure conditions were used for five laboratory animal species (unanesthetized) for a wide range of particle sizes. Deposition efficiency was calculated as a function of an impaction parameter, $d_{ae}^2 Q$ for ET deposition, where d_{ae} is aerodynamic particle diameter and Q is the flow rate estimated as the species-specific minute volume $(\dot{V}_E)/30$. Deposition efficiency in the TB and PU regions was estimated as a function of d_{ae}. The calculated efficiencies are adjusted for inhalability to produce predicted deposition fractions for various regions of the respiratory tract (USEPA, 1994a). The geometric standard deviation of the particle diameter distribution is also an input parameter. Thus, major determinants of particle deposition such as species-specific ventilation rates, particle diameter, and distribution are used in the default model. Localized deposition (e.g., carinal versus bronchoalveolar junction) cannot be estimated because available deposition data are such that only the three major regions of the respiratory tract can be defined. Nevertheless, Figure 2 illustrates that application of the default DAF$_r$ for particles is a significant factor in accounting for species differences in deposition. For example, if the four species depicted in Figure 4 were all exposed to the same aerosol concentration of 100 mg/m³, application of the species-specific DAF$_{PU}$ to this exposure level results in different HEC estimates for the different species at various particle diameters. The HEC estimate for the hamster would be the lowest

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[2] Although the term Physiologically Based Pharmacokinetic Modeling (PBPK) is often used in a general sense, dosimetry modeling is used in this presentation as a more comprehensive term to capture not only model structures used to address volatile organic chemicals, but also irritant gases and particles. Mathematical modeling is defined as the use of the physical laws of mass, heat, and momentum conservation to quantify the dynamics of a system of interest (e.g., particle deposition and clearance). Dosimetry modeling is defined as the application of mathematical modeling to characterize mechanistic determinants of exposure-dose-response.

(29mg/m³) at an MMAD = .9 µm and σ_g = 1.3. However, the rat would have the lowest HEC (2.2 mg/m³) at an MMAD = 5 µm and σ_g = 1.3.

The default DAF, calculated for gases, as for particles, is different for each respiratory tract region or for remote effects. In addition, the DAF, for gases is dependent on which of three categories classifies the gas. The scheme used to categorize gases (Figure 3) was constructed based on the physicochemical characteristics of water solubility and reactivity as major determinants of gas uptake. Reactivity is defined to include both the propensity for dissociation and the ability to react either spontaneously or via enzymatic reaction in the respiratory tract. The scheme does not apply to stable gases that exert their effects by reversible "physical" interactions of gas molecules with biomolecules (e.g., "displacement" of oxygen by carbon dioxide).

As an example, Figure 4 shows the schematic for the default model used to characterize respiratory tract uptake of Category 1 gases. Category 1 gases are defined as highly water soluble and rapidly reactive. Because of these properties, Category 1 gases (e.g., hydrogen fluoride, chlorine, formaldehyde, and the organic esters) are likely to interact with the respiratory tract. The objective of the default modeling approach is to describe the effective dose to the three regions by
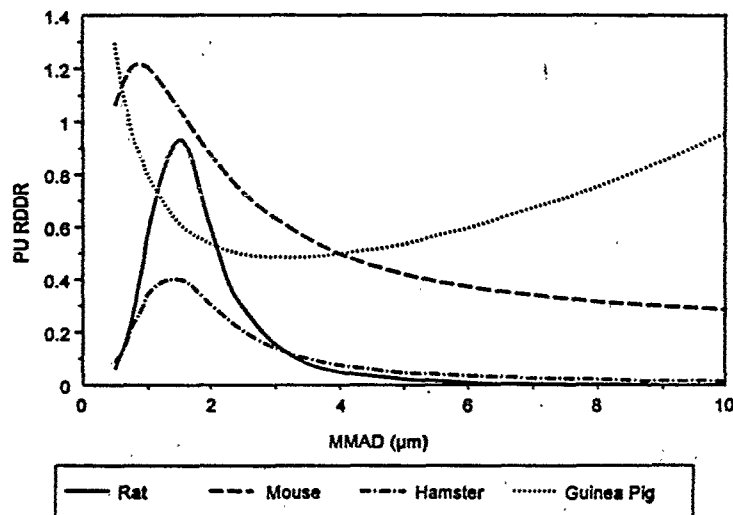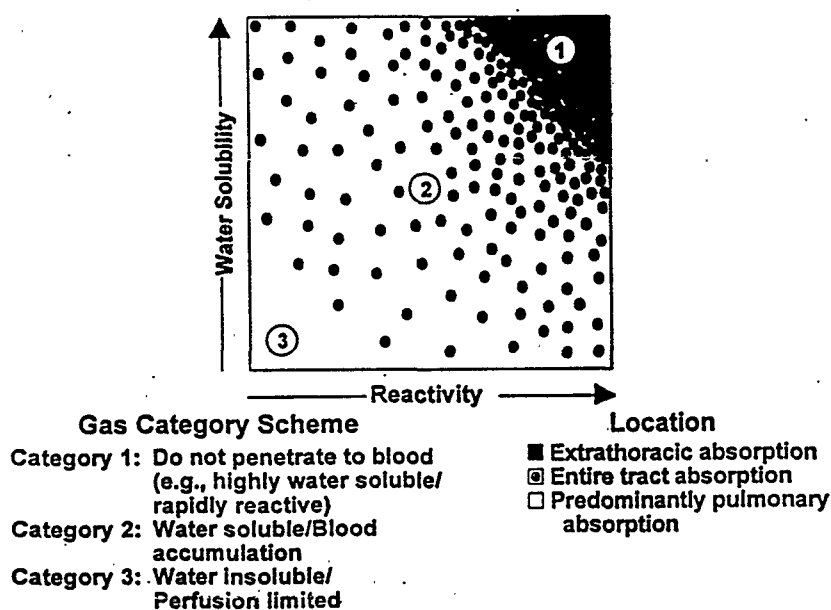

Figure 2. Regional Deposited Dose Ratio (RDDR) for the PU region shown for rat, mouse, hamster, and guinea pig. Estimates calculated using the default particle deposition model and default parameters for species-specific ventilation rates and PU region surface areas as provided elsewhere (USEPA, 1994a). The RDDR would be used in Equation 2 as the DAF, to calculate the human equivalent concentration for an effect of inhaled particles in the PU region. MMAD = mass median aerodynamic diameter, σ_g = geometric standard deviation of particle distribution.

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addressing the absorption or "scrubbing" of the gas from the inspired airstream as it travels from the ET to PU region. The approach used to model the uptake is based on the concept of an overall mass transfer coefficient, K_g (USEPA, 1994a). The concept of the K_g is based on a concentration gradient analysis similar to Fick's law of diffusion, and is utilized to describe transport through several different phases, such as air and the liquid/tissue phase of the respiratory tract. A fractional penetration model is used to determine the fraction of the inhaled concentration in each region. For example, the uptake in the ET region and the output to the TB region (fractional penetration, fp_{ET}) is dependent on the K_{gET}, so that uptake in the ET region is defined as $1-fp_{ET}$. A ventilation-perfusion model is used to estimate the uptake in the PU region by substituting the concentration of the air exiting the TB region for the inhaled concentration. The rate of mass absorbed at the gas-surface interface of the airway in a region (r) is simply the product of the absorbed fraction, $(1-fp_r)$, and the total mass inhaled during a single breath, $\dot{V}_E C_i$, where C_i is the inhaled concentration. The $\dot{V}_E$ is used as the default volumetric flow rate because it approximates the flow rate at which the animal was breathing during the experimental exposure. The alveolar ventilation rate is used to calculate the absorption rate for the PU region.

Gas Category Scheme

Category 1: Do not penetrate to blood
(e.g., highly water soluble/
rapidly reactive)
Category 2: Water soluble/Blood
accumulation
Category 3: Water insoluble/
Perfusion limited

Location

■ Extrathoracic absorption
▣ Entire tract absorption
☐ Predominantly pulmonary
absorption

Figure 3. Gas categorization scheme based on water solubility and reactivity as major determinants of gas uptake (USEPA, 1994a). Reactivity is defined to include both the propensity for dissociation as well as the ability to react either spontaneously or via enzymatic reaction in the respiratory tract. Definitive characteristics of each category and the anticipated location (region) for respiratory tract uptake are shown.
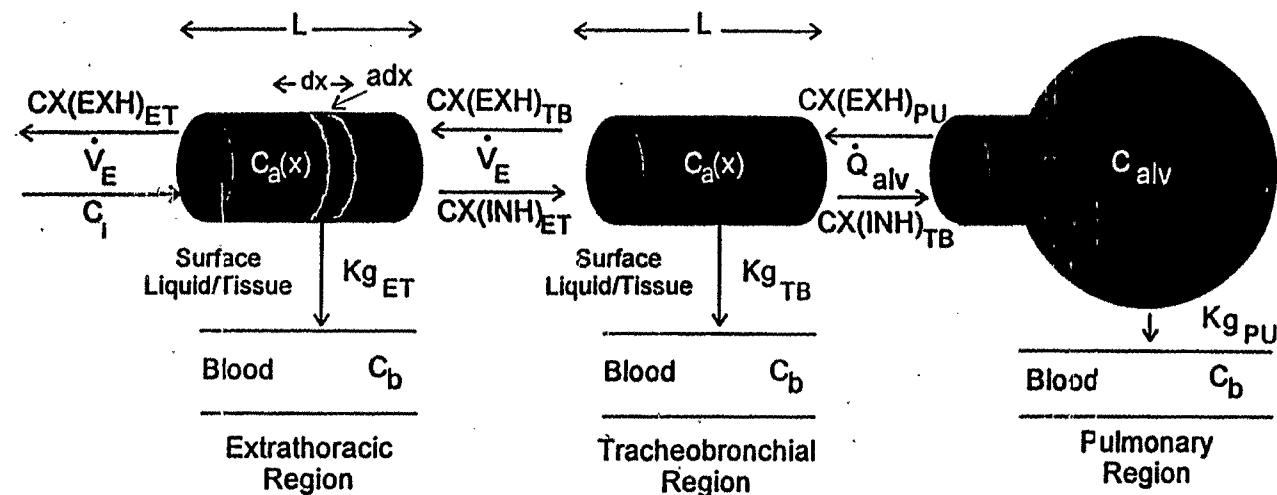
Figure 4. Schematic of model to estimate default DAF_r for gases in Category 1 (USEPA,1994a). a = Airway perimeter; C_{alv} = Pulmonary region gas concentration; C_b = Blood concentration; C_i = Inhaled concentration; $CX(EXH)_{ET}$ = Concentration exiting from ET region upon exhalation; $CX(EXH)_{PU}$ = Concentration exiting from PU region upon exhalation; $CX(EXH)_{TB}$ = Concentration exiting from TB region upon exhalation; $CX(INH)_{ET}$ = Concentration exiting from ET region upon inhalation; $CX(INH)_{TB}$ = Concentration exiting from TB region upon inhalation; dx = Differential of axial distance into airway; ET = Extrathoracic respiratory region; K_{gET} = Overall mass transport coefficient of the ET region; K_{gPU} = Overall mass transport coefficient of the PU region; K_{gTB} = Overall mass transport coefficient of the TB region; PU = Pulmonary respiratory tract region; $\dot{Q}_{alv}$ = Alveolar ventilation rate; TB = Tracheobronchial respiratory tract region; V_E = Minute ventilation.

Table 3. Heirarchy of Model Structures for Dosimetry and Interspecies Extrapolation

Optimal[1] Model Structure

Structure describes all significant mechanistic determinants of chemical dispositions, toxicant-target interaction, and tissue response

Use chemical-specific and species-specific parameters

Dose metric described at level of detail commensurate to toxicity data

Default Model Structure

Limited or default description of mechanistic determinants of chemical dispositions, toxicant-target interaction, and tissue response

Uses categorical or default values for chemical and species parameters

Dose metric at generic level of detail

[1]Optimal is defined as preferable or more appropriate relative to the default.

The DAF_r for each region is then calculated based on equations describing the relationship between K_g and $1-fp_r$ for each region, the ventilation rate, and regional surface area. The assumption that absorption is distributed equally within a region allows the description on a regional basis. Although this is a drastically reduced number of parameters in comparison to distributed parameter model descriptions, the default model does require regional K_g values for different animal species and gases. It is important to note that the Kg is both species- and chemical-specific. Values of K_g obtained in a single animal species may be scaled within a species for a different gas in the same category by decomposing K_g to the individual gas-phase and surface-liquid/tissue phase transport resistances (Jarabek, 1995b). The default equations can be further reduced by applying additional simplifying assumptions regarding the likely values of K_g. The derivation of the equations and DAF_r for each region, including the models for the two other gas categories, are provided in detail elsewhere (USEPA, 1994a).

An understanding of the basis for the default adjustments allows development of a framework for the evaluation of whether an alternative model structure that incorporates more mechanistic data may be considered optimal relative to the default. Depending on the relative importance of various mechanistic determinants, models with less detail (*i.e.*, less of the determinants depicted in Figure 1) may be used to adequately describe difference in dosimetry for the purposes of interspecies extrapolation. An alternative model might be considered more appropriate than the default for extrapolation when default assumptions or parameters are replaced by a more detailed, biologically motivated description or actual data. For example, a model could be preferable if it incorporates more chemical- or species-specific information, or if it accounts for more mechanistic determinants. These considerations are summarized in Table 3. The sensitivity of the model to these differences in structure may be gauged by its relative importance in describing the

response function for a given chemical. A model that incorporates many parameters may not be any better at describing ("fitting") limited response data than would a simpler model. In these instances, the principle of parsimony might dictate the use of a simpler model. Woodruff *et al.* (1992) have used Monte Carlo analyses to assess the impact that structure and parameterization of PBPK models have on model output predictions and variability. An excessive number of parameters was shown to lead to overparameterization, and cause large variability in the output.

IMPACT OF DOSIMETRY ADJUSTMENT ON THE INTERSPECIES UF

As noted in Table 2, the default UF for interspecies extrapolation to derive an inhalation RfC is approximately 3-fold, rather than the general 10-fold. The 10-fold factor was supported by empiric data showing a lognormal distribution of effect levels from various species. The "halving" (or 10^5) of the standard UF was based on the concept that the default dosimetry model structures were accounting for the "pharmacokinetic" portion of the interspecies variability for which the UF was applied. A similar approach to parceling the overall magnitude of the intraspecies or intrahuman (10H) and interspecies (10A) UFs into pharmacokinetic (toxicokinetic) and pharmacodynamic (toxicodynamic) components was proposed by Renwick (1993). Figure 5 shows the values of the parcels proposed. The EPA uses 3.16 for each pharmacokinetic and pharmacodyamic parcel. Renwick (1993), based on an analysis of oral pharmacologic data, ascribed more variability to the pharmacokinetic portion (a factor of 4 for pharmacokinetics versus 2.5 for pharmacodynamics). Figure 6 inserts the EPA UF scheme for derivation of inhalation RfCs into the overall framework for comprehensive exposure-dose-response description. Because default adjustments are used in the RfC derivation, the "pharmacokinetic" portion of the intraspecies UF (10H) was not obviated. Although the default dosimetric adjustments do adjust for factors that control delivered doses in humans, a portion of the uncertainty remains because the adjustments are viewed as default. More robust dosimetry models can be anticipated to obviate the entire pharmacokinetic component of the UF. Likewise, models that address the determinants of response may impact the 10H UF. It is recognized that there are limited data on variability of pharmacodynamics which are not confounded by the presence of pharmacokinetic variability; *i.e.*, as acknowledged earlier, the UFs are not entirely independent and thus, in this case, the vertical demarcation between pharmacokinetic and pharmacodynamic processes is not entirely distinct, nor would these processes necessarily be distinct horizontally between inter- and intraspecies variability.

Reduction of the 10A UF was also supported by some empirical analyses of inhalation data. Jarabek and Hasselblad (1991) showed that the deviation across species and chemicals for HEC estimates derived using the interim 1990 EPA methods was reduced by approximately 2-fold versus that of using previous (*Federal Register*, 1980) methods. The average absolute difference between estimates for different species with comparable (with respect to exposure duration and severity level, *e.g.*, subchronic LOAELs were only compared to subchronic LOAELs) toxicity data were compared across 22 chemicals. The average variation between

	Pharmacokinetic	Pharmacodynamic
Interspecies (10A)	1 (4.0)	3.16 (2.5)
Intraspecies (10H)	3.16 (4.0)	3.16 (2.5)

Figure 5. Pharmacokinetic and pharmacodynamic components of the interspecies (10A) and intraspecies or intrahuman (10H) UFs as applied in the RfC methods (USEPA, 1994a). Default values for the magnitude of each is provided. Values for the same components proposed by Renwick (1993) are shown in parentheses.
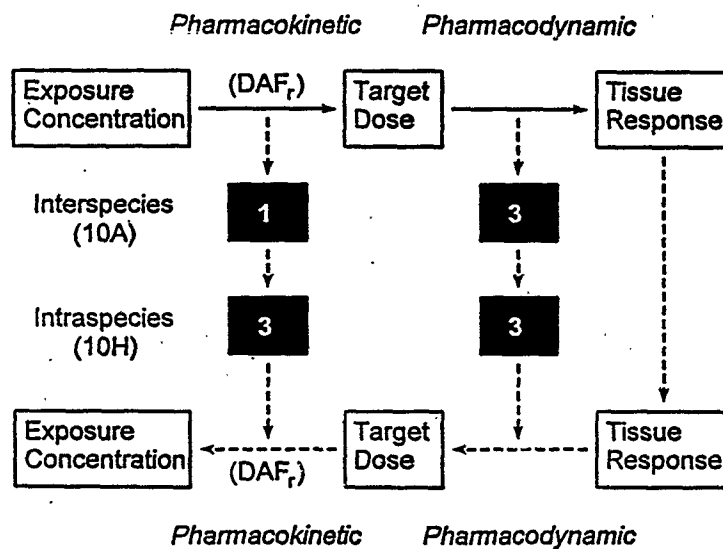

Figure 6. Interspecies (10A) and intraspecies or intrahuman (10H) UFs as applied in the RfC methods (USEPA, 1994a) are shown incorporated into the framework of exposure-dose-response continuum. Dashed line indicate extrapolation. Modified from Andersen, Clewell, and Krishnan (1995).

HEC estimates (4.0) remained the same when separated into analysis for respiratory versus remote effects, whereas the average variation between estimates using the previous methods was 5.0 and 17.0, respectively. The default dosimetric adjustments for remote effects of Category 3 gases were also shown to be consistently less than those calculated with previous methods by a factor of 3 for rats and 6 for mice (Jarabek *et al.*, 1990; Overton and Jarabek, 1989 a, b).

The rationale for the reduction in the UF for interspecies extrapolation is essentially semi-empirical. The UF to date has been based on analyses of effect levels which were not at the level of mechanistic detail that contemporary assays provide. As illustrated by the simplifying assumptions that were necessary to invoke in order to create default dosimetry adjustments commensurate with the available data on most chemicals, the database on mechanistic determinants of dosimetry (pharmacokinetics) and response (pharmacodynamics) is not yet sufficiently large to serve as the basis of comprehensive analyses of variability across large numbers of chemicals. Because of the differences in key determinants of dosimetry for different types of chemicals (*e.g.*, Category 1 gas versus Category 3 gas), and for different types of toxicity (*e.g.*, respiratory tract versus remote effects), future mechanistic-based UFs, if not chemical-specific, will likely be different for chemical category and toxicity. Nevertheless, the framework is useful in that it provides for flexible UFs and emphasizes how data on key determinants along the exposure-dose-response continuum can increase the accuracy of required extrapolations. The framework is developed "piece-by-piece" because this is how mechanistic data are developed and this also overlaps with the components of the UFs.

Emphasis should be placed on the fact that the interfaces between exposure concentration and target tissue dose are not necessarily linear, depending on the processes involved. This is why dosimetry models that integrate these factors are preferred because nonlinearities are readily addressed. Some of the default equations do account for nonlinearities, and this is an important distinction from approaches such as that of Lewis, Lynch, and Nikiforov (LLN) (1990), which appropriately advocates adjustment for physiological parameters, but does not take into account mechanistic determinants of uptake. The LLN approach uses adjustments for scaling (S), interspecies differences in response (R), and an additional factor intended to reflect the residual uncertainty (U) in the evaluator's mind after arriving at the best estimates for S and R. Interspecies comparisons that rely only on the available chemical-specific database can be greatly influenced by differences in study design. For example, comparison between two species when the toxicity is assayed differently is likely to be more a function of the variability in the end point than differences in pharmacokinetics between species. Systematic development across species of data on key determinants of uptake can alleviate such assay dependence. Andersen, Clewell, and Krishnan (1995) submit that scaling factors for interspecies extrapolation were based on studies of administered dose, whereas physiologically-based applications now allow for reevaluation of the biological motivation for the interspecies extrapolation UF to include dosimetry and tissue responsiveness. As can be appreciated by the default structures, good data on fundamental anatomic and physiologic parameters are still required. It is hoped that mechanistic approaches will stimulate fulfillment of the required data gaps.

ADDITIONAL APPLICATIONS FOR MECHANISTIC DATA

Both the duration adjustment shown in Equation 1 and the various UFs applied will benefit from more robust application of comprehensive, biologically motivated model structures to the subject extrapolations. Short of constructing chemical-specific comprehensive models, however, the iterative framework shown in Figure 1 allows for the identification of key processes and parameters that may be useful to interpretation of the available data and reduce the applied UFs. As more mechanistic data on determinants of the components along the exposure-dose-response continuum become available, their evaluation will likely refine and modify the UFs applied.

One example of the use of mechanistic data was provided in the discussion of required database. Another is the use of BMD analyses to obviate the requirement for the LOAEL to NOAEL extrapolation. Because dosimetry models incorporate concentration-and time-dependent processes (*e.g.*, rate of metabolism) in a species-dependent manner, the duration adjustment (Equation 1) could be obviated, and depending on the description, could also impact the magnitude of the interspecies and intraspecies UFs. Data on the mechanism of action can be used to determine whether the $(C \times t)$ adjustment (Equation 1) is appropriate. Choice of the dose metric should be based on an understanding of the mechanism of action for the effect under consideration (Jarabek, 1995a). For example, extrapolation based on C alone may be appropriate for irritants. The nature of the pathogenesis can be used to determine if a UF is needed for extrapolation of subchronic to chronic data. In this example, if the chemical or its damage can accumulate over time, then a UF should be applied to extrapolate a 90-day study for purposes of calculating a lifetime estimate. Studies on the dynamics of repair would be useful to determining whether the UF for extrapolation of subchronic data was necessary.

In vitro research strategies could provide information critical to assessing the variability of sensitivity to chemical injury of cells from different species. This information would improve characterization of the pharmacodynamic portion of the intraspecies and interspecies UFs.

BMD analyses are now advocated for both noncancer and cancer assessments (Barnes *et al.*, 1995; USEPA, 1994b, 1995). A nonlinear approach to cancer assessment based on an understanding of the mode of action for a chemical has also been proposed (USEPA, 1994b). Emphasis should be placed on how different end points that serve as the basis of these assessments fall along the pathogenesis continuum. For example, how should estimates derived on the end points of epithelial hyperplasia, erosion, subsequent cellular proliferation, and tumor incidence be related to one another? Mechanistic data on determinants of tissue response may afford the opportunity to rectify approaches to noncancer versus cancer assessment *i.e.*, relate the toxicities and derive one estimate rather than separate ones for noncancer versus cancer toxicity.

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SUMMARY

Mechanistic data help describe the major factors influencing chemical disposition and toxicant-target tissue interactions, and should increase the accuracy of exposure-dose-response assessment. A framework that allows for the iterative incorporation of mechanistic data as they become available will ensure that extrapolations required in such assessments are commensurate with the state-of-the-science. The development of the dosimetry adjustments by the EPA is viewed as an approach that embarks on the use of mechanistic data with concomitant modification of the UF for interspecies extrapolation. As more mechanistic data on determinants of the components along the exposure-dose-response continuum become available, their evaluation will likely refine and modify the UFs applied.

Note

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